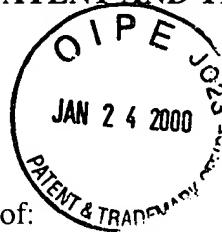


IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



Group Art Unit: 1615

Examiner: Gollamudi S. Kishore

In re PATENT REISSUE APPLICATION of:

Patentees : Yong WEI et al.)
U.S. Patent No. : 5,681,589)
Issued : October 28, 1997)
Reissue Application No. : TBD)
Reissue Filed :)
For : LIPOSOMAL CERAMIDE-RELATED)
COMPOUNDS AND THE)
THERAPEUTIC USE THEREOF)
Attorney Docket : TLC 144C RIS)

**DECLARATION AND
POWER OF ATTORNEY**

Date:

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

We, Yong Wei, Eric Mayhew, Imran Ahmad and Andrew S. Janoff, DECLARE:

That we are citizens of the People's Republic of China, United Kingdom, India, and the United States, respectively, and that our post office addresses are, respectively:

Yong Wei, 39 Seneca Trail, Branchburg, NJ 08876

Eric Mayhew, 3905 West Beretona Street, Seattle, WA 98199

Imran Ahmad, 2408 Fox Run Drive, Plainsboro, NJ 08536

Andrew S. Janoff, 560 Countess Drive, Yardley, PA, 19067, US

That we verily believe ourselves to be the original, first and joint inventors of the invention LIPOSOMAL CERAMIDE-RELATED COMPOUNDS AND THE THERAPEUTIC USE THEREOF described and claimed in the United States Letters Patent No. 5,681,589 issued October 28, 1999 on application no. 545,164, filed October 19, 1995;

That we have reviewed and understood the contents of the reissue specification including the claims.

That we acknowledge our duty to disclose information of which we are aware which is material to the examination of this application under Rule 56(a);

We verily believe that the original United States Letters Patent No. 5,681,589, referred to above, is wholly or partly inoperative because the patentees claimed less than they had a right to claim. The specific errors relied upon are the failure to present the following claims:

16. A compound having the formula R¹-Y¹-CHZ¹-CH(NY²Y³)-CH₂-Z², wherein:

R¹ is a straight-chained alkyl, alkenyl or alkynyl group having from 5 to 19 carbon atoms in the aliphatic chain;

Y¹ is -CH=CH-, -C≡C- or -CH(OH)CH(OH)-;

Z¹ is OH or a phosphorylcholine attachment-inhibiting group selected from the group consisting of -X¹, -OX¹, -X²X³ and -OX²X³;

Y² is H, a phenyl group, an alkyl-substituted phenyl group having from 1 to about 6 carbons in the alkyl chain, or an alkyl chain having from 1 to 10 carbons;

Y³ is H or a group having the formula -C(O)R² or -S(O)₂R²;

R² is a straight-chained alkyl moiety selected from the group consisting of -(CH₂)₃CH₃, -(CH₂)₅CH₃, -(CH₂)₇CH₃ and -(CH₂)₉CH₃, an alkenyl group having from 1 to 23 carbon atoms in the aliphatic chain and an alkynyl group having from 1 to 23 carbon atoms in the aliphatic chain;

Z² is OH or a phosphorylcholine attachment-inhibiting group selected from the group consisting of -X¹, -OX¹, -X²X³ and -OX²X³;

X¹ is selected from the group consisting of -C(O)H, -CO₂H, CH₃(C(CH₃)₃)₂, Si(C(CH₃)₃)₃, Si(PO₄)₂C(CH₃)₃, a phenyl group, an alkyl-substituted phenyl group having from 1 to 6 carbons in the alkyl chain, an alkyl chain having from 1 to 6 carbons, an amino group, a fluorine, a chlorine, and a group having the formula C(R³R⁴)OH;

X^2 is selected from the group consisting of CH_2 -, $\text{C}(\text{CH}_3)_2$ -, $\text{Si}(\text{PO}_4)_2$ -, $\text{Si}(\text{CH}_3)_2$ -, SiCH_3PO_4 -,

$\text{C}(\text{O})$ - and $\text{S}(\text{O})_2$ -;

X^3 is selected from the group consisting of $-\text{C}(\text{O})\text{H}$, $-\text{CO}_2\text{H}$, $-\text{CH}_3$, $-\text{C}(\text{CH}_3)_3$, $-\text{Si}(\text{CH}_3)_3$, $-\text{SiCH}_3(\text{CH}_3)_2$, $-\text{Si}(\text{CH}_3)_3$, $-\text{Si}(\text{PO}_4)_2\text{C}(\text{CH}_3)_3$, a phenyl group, an alkyl-substituted phenyl group having from 1 to 6 carbons in the alkyl chain, an alkyl chain having from 1 to 6 carbons, an amino moiety, a chlorine, a fluorine, or a group having the formula $\text{C}(\text{R}^3\text{R}^4)\text{OH}$, wherein each of R^3 and R^4 is independently an alkyl chain having from 1 to 6 carbons, a phenyl group or an alkyl-substituted phenyl group having from 1 to 6 carbons in the alkyl chain;

wherein when Z^2 is an amino group, R^2 is an aliphatic chain having from 1 to 9 or from 19 to 23 carbon atoms in the aliphatic chain.

17. The compound of claim 16, wherein R^2 is an alkyl chain.

18. The compound of claim 16, wherein R^1 is $\text{CH}_3(\text{CH}_2)_12$.

19. The compound of claim 16, wherein Y^1 is $-\text{CH}=\text{CH}-$.

20. The compound of claim 16, wherein Y^2 is H .

21. The compound of claim 16, wherein Y^3 is $-\text{C}(\text{O})\text{R}^2$.

22. The compound of claim 16, wherein Z^1 is OH .

23. The compound of claim 22, wherein Z^2 is a group having the formula $-\text{X}^2\text{X}^3$ or $-\text{O}-\text{X}^2\text{X}^3$.

24. The compound of claim 23, wherein Z^2 is $-\text{OC}(\text{O})\text{CH}_3$, $-\text{OC}(\text{O})\text{CH}_2\text{CH}_2\text{CH}_3$, $-\text{OC}(\text{O})\text{CH}(\text{CH}_3)\text{CH}_3$, or $-\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$.

25. The compound of claim 24, wherein Z^2 is $-\text{OSi}(\text{CH}_3)_2\text{C}(\text{CH}_3)_3$.

26. The compound of claim 22, wherein Z² is a group having the formula -X¹ or -OX¹.

27. The compound of claim 16 having the formula CH₃(CH₂)₁₂-CH=CH-CH₂Z¹-CH(NHY³)-CH₂-Z².

28. The compound of claim 27, wherein Z¹ is OH and Y³ is a group having the formula -C(O)R².

29. The compound of claim 28, wherein Y³ is -C(O)(CH₂)₄CH₃.

30. The compound of claim 27, wherein Z² is -OSi(CH₃)₂C(CH₃)₃, -OSi(PO₄)₂C(CH₃)₃, -C(O)CH₃ or -OC(O)CH₂CH₂CH₃.

31. A pharmaceutical composition comprising the compound of claim 16.

32. A liposome having a bilayer comprising a lipid component, said lipid component comprising at least about 5 mole percent of the compound of claim 16.

We hereby appoint the following attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: Rosanne Goodman (Reg. No. 32,534) and Russell Lindenfeldar (Reg. No. 39,750) at The Liposome Company, Inc., One Research Way, Princeton, New Jersey, 08540, Telephone: (609) 452,7060, Telefax: (609) 734-0882. Address all correspondence to THE LIPOSOME COMPANY, INC. One Research Way, Princeton Forrestal Center, Princeton, NJ 08520.

The undersigned hereby authorize the U.S. attorneys named herein to accept and follow instructions from the undersigned assignee, if any, and/or, if the undersigned is not a resident of the United States, the undersigned's domestic attorney, patent attorney or patent agent, as to any action to be taken in the Patent and Trademark Office regarding this application without direct communication between the U.S. attorneys and the undersigned. In the even of a change in the person(s) from whom instructions may be taken, the U.S. attorneys named herein will be so notified by the undersigned.

The undersigned declare further that all statements made herein of their own knowledge are true and that all statements made on information and belief are believed to be true; and

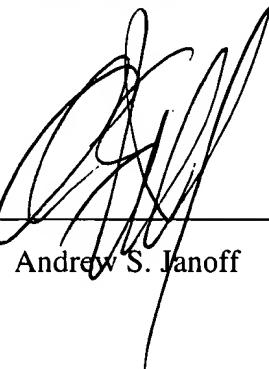
Further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

Date: _____ By: _____
Yong Wei

Date: 5/Nov/99 By: 
Eric Mayhew

Date: 11/11/99 By: Imran Ahmad
Imran Ahmad

Date: 11/11/99 By: 
Andrew S. Janoff

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



Group Art Unit: 1615

Examiner: Gollamudi S. Kishore

In re PATENT REISSUE APPLICATION of:

Patentees : Yong WEI et al.)
U.S. Patent No. : 5,681,589)
Issued : October 28, 1997)
Reissue Application No. : TBD)
Reissue Filed :)
For : LIPOSOMAL CERAMIDE-RELATED) COMPOUNDS AND THE) THERAPEUTIC USE THEREOF)
Attorney Docket : TLC 144C RIS)

**DECLARATION AND
POWER OF ATTORNEY**

Date:

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

We, Yong Wei, Eric Mayhew, Imran Ahmad and Andrew S. Janoff, DECLARE:

That we are citizens of the People's Republic of China, United Kingdom, India, and the United States, respectively, and that our post office addresses are, respectively:

Yong Wei, 39 Seneca Trail, Branchburg, NJ 08876

Eric Mayhew, 3905 West Beretona Street, Seattle, WA 98199

Imran Ahmad, 2408 Fox Run Drive, Plainsboro, NJ 08536

Andrew S. Janoff, 560 Countess Drive, Yardley, PA, 19067, US

That we verily believe ourselves to be the original, first and joint inventors of the invention LIPOSOMAL CERAMIDE-RELATED COMPOUNDS AND THE THERAPEUTIC USE THEREOF described and claimed in the United States Letters Patent No. 5,681,589 issued October 28, 1999 on application no. 545,164, filed October 19, 1995;

That we have reviewed and understood the contents of the reissue specification including the claims.

That we acknowledge our duty to disclose information of which we are aware which is material to the examination of this application under Rule 56(a);

We verily believe that the original United States Letters Patent No. 5,681,589, referred to above, is wholly or partly inoperative because the patentees claimed less than they had a right to claim. The specific errors relied upon are the failure to present the following claims:

16. A compound having the formula $R^1-Y^1-CHZ^1-CH(NY^2Y^3)-CH_2-Z^2$, wherein:

R^1 is a straight-chained alkyl, alkenyl or alkynyl group having from 5 to 19 carbon atoms in the aliphatic chain;

Y^1 is $-CH=CH-$, $-C\equiv C-$ or $-CH(OH)CH(OH)-$;

Z^1 is OH or a phosphorylcholine attachment-inhibiting group selected from the group consisting of $-X^1$, $-OX^1$, $-X^2X^3$ and $-OX^2X^3$;

Y^2 is H, a phenyl group, an alkyl-substituted phenyl group having from 1 to about 6 carbons in the alkyl chain, or an alkyl chain having from 1 to 10 carbons;

Y^3 is H or a group having the formula $-C(O)R^2$ or $-S(O)_2R^2$;

R^2 is a straight-chained alkyl moiety selected from the group consisting of $-(CH_2)_3CH_3$, $-(CH_2)_5CH_3$, $-(CH_2)_7CH_3$ and $-(CH_2)_9CH_3$, an alkenyl group group having from 1 to 23 carbon atoms in the aliphatic chain and an alkynyl group having from 1 to 23 carbon atoms in the aliphatic chain;

Z^2 is OH or a phosphorylcholine attachment-inhibiting group selected from the group consisting of $-X^1$, $-OX^1$, $-X^2X^3$ and $-OX^2X^3$;

X^1 is selected from the group consisting of $-C(O)H$, $-CO_2H$, $CH_3(C(CH_3)_3)_2$, $Si(C(CH_3)_3)_3$, $Si(PO_4)_2C(CH_3)_3$, a phenyl group, an alkyl-substituted phenyl group having from 1 to 6 carbons in the alkyl chain, an alkyl chain having from 1 to 6 carbons, an amino group, a fluorine, a chlorine, and a group having the formula $C(R^3R^4)OH$;

X^2 is selected from the group consisting of CH_2 -, $C(CH_3)_2$ -, $Si(PO_4)_2$ -, $Si(CH_3)_2$ -, $SiCH_3PO_4$ -,

$C(O)$ - and $S(O)_2$ -;

X^3 is selected from the group consisting of $-C(O)H$, $-CO_2H$, $-CH_3$, $-C(CH_3)_3$, $-Si(CH_3)_3$, $-SiCH_3(C(CH_3)_3)_2$, $-Si(C(CH_3)_3)_3$, $-Si(PO_4)_2C(CH_3)_3$, a phenyl group, an alkyl-substituted phenyl group having from 1 to 6 carbons in the alkyl chain, an alkyl chain having from 1 to 6 carbons, an amino moiety, a chlorine, a fluorine, or a group having the formula $C(R^3R^4)OH$, wherein each of R^3 and R^4 is independently an alkyl chain having from 1 to 6 carbons, a phenyl group or an alkyl-substituted phenyl group having from 1 to 6 carbons in the alkyl chain;

wherein when Z^2 is an amino group, R^2 is an aliphatic chain having from 1 to 9 or from 19 to 23 carbon atoms in the aliphatic chain.

17. The compound of claim 16, wherein R^2 is an alkyl chain.

18. The compound of claim 16, wherein R^1 is $CH_3(CH_2)_12$ -.

19. The compound of claim 16, wherein Y^1 is $-CH=CH-$.

20. The compound of claim 16, wherein Y^2 is H.

21. The compound of claim 16, wherein Y^3 is $-C(O)R^2$.

22. The compound of claim 16, wherein Z^1 is OH.

23. The compound of claim 22, wherein Z^2 is a group having the formula $-X^2X^3$ or $-O-X^2X^3$.

24. The compound of claim 23, wherein Z^2 is $-OC(O)CH_3$, $-OC(O)CH_2CH_2CH_3$, $-OC(O)CH(CH_3)CH_3$, or $-OSi(CH_3)_2C(CH_3)_3$.

25. The compound of claim 24, wherein Z^2 is $-OSi(CH_3)_2C(CH_3)_3$.

26. The compound of claim 22, wherein Z² is a group having the formula -X¹ or -OX¹.

27. The compound of claim 16 having the formula CH₃(CH₂)₁₂-CH=CH-CH₂Z¹-CH(NHY³)-CH₂-Z².

28. The compound of claim 27, wherein Z¹ is OH and Y³ is a group having the formula -C(O)R².

29. The compound of claim 28, wherein Y³ is -C(O)(CH₂)₄CH₃.

30. The compound of claim 27, wherein Z² is -OSi(CH₃)₂C(CH₃)₃, -OSi(PO₄)₂C(CH₃)₃, -C(O)CH₃ or -OC(O)CH₂CH₂CH₃.

31. A pharmaceutical composition comprising the compound of claim 16.

32. A liposome having a bilayer comprising a lipid component, said lipid component comprising at least about 5 mole percent of the compound of claim 16.

We hereby appoint the following attorneys to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: Rosanne Goodman (Reg. No. 32,534) and Russell Lindenfeldar (Reg. No. 39,750) at The Liposome Company, Inc., One Research Way, Princeton, New Jersey, 08540, Telephone: (609) 452,7060, Telefax: (609) 734-0882. Address all correspondence to THE LIPOSOME COMPANY, INC. One Research Way, Princeton Forrestal Center, Princeton, NJ 08520.

The undersigned hereby authorize the U.S. attorneys named herein to accept and follow instructions from the undersigned assignee, if any, and/or, if the undersigned is not a resident of the United States, the undersigned's domestic attorney, patent attorney or patent agent, as to any action to be taken in the Patent and Trademark Office regarding this application without direct communication between the U.S. attorneys and the undersigned. In the event of a change in the person(s) from whom instructions may be taken, the U.S. attorneys named herein will be so notified by the undersigned.

The undersigned declare further that all statements made herein of their own knowledge are true and that all statements made on information and belief are believed to be true; and

Further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Respectfully submitted,

Date: 1/5/2000

By: 
Yong Wei

Date: _____

By: _____

Eric Mayhew

Date: _____

By: _____

Imran Ahmad

Date: _____

By: _____

Andrew S. Janoff